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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/219,442	12/23/1998	JING-SHAN HU	PF112P2D1	4797

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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	37

DATE MAILED: 04/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/219,442	HU ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-132,145-304 and 368-446* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 34 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims withdrawn from consideration are 45-52,65-72,85-92,105-112,125-132,157-164,177-184,197-204,217-224,237-244,257-264,277-284,297-366,379-386,399-406 and 419-426.

Continuation of Disposition of Claims: Claims rejected are 33-44,53-64,73-84,93-104,113-124,145-156,165-176,185-196,205-216,225-236,245-256,265-276,285-296,367-378,387-398,407-418 and 427-438.

DETAILED ACTION

1. Formal Matters

A. The Information Disclosure Statement, filed 8/16/02, has been entered into the record.

B. The Information Disclosure Statement, filed 2/3/03, has been entered into the record.

C. Claims 33-132, 145-304 and 368-446 were pending in this Office Action. In Amendment C, filed 2/3/03, Applicants canceled claims 133-144 and 305-366. Therefore, claims 33-44, 53-64, 73-84, 93-104, 113-124, 145-156, 165-176, 185-196, 205-216, 225-236, 245-256, 265-276, 285-296, 367-378, 387-398, 407-418 and 427-438 are the subject of this Office Action.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Rejoining of Method Claims

A. Applicants request that the withdrawn method claims be rejoined upon notification of allowable product claims. Method claims will be rejoined insofar as they are commensurate in scope with the allowed product claims and do not raise any rejections under 35 USC 112.

3. Information Disclosure Statement

A. Applicants have submitted an Information Disclosure Statement (Paper No. 34). They argue that Statutory Declarations as well as reference of an International Search Report (filed March 12, 2002; Paper No. 25) are proper subject matter for an IDS. Though the Examiner has considered these Declarations and Report, they are not proper subject matter for an IDS. If Applicants wish the references of the search report be initialed, then these references themselves should be cited on the IDS.

4. Claim Objections

A. Claims 245, 285, 407 and 427 are objected to since the syntax of the phrase "a protein fragment encoded by the cDNA contained in ATCC" could be improved since it appears that the ATCC clone only contains a fragment of the full-length VEGF-2 protein.

5. Double Patenting

A. Claims 33-44, 53-64, 73-84, 93-104, 113-124, 145-156, 165-176, 185-196, 205-216, 225-236, 245-256, 265-276, 285-296, 367-378, 387-398, 407-418 and 427-438 remain provisionally rejected as being obvious over U.S. Applications 09/257,272, 09/935,726 and 09/107,997. Applicants have stated that they will file a Terminal Disclaimer once allowable subject matter has bee determined. 09/623,725 is abandoned.

Regarding 09/107,997 and 09/257,272, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 33-132, 145-304 and 367-446 are provisionally rejected as being obvious over the following applications in anticipation of the method claims being rejoined with the protein claims of the present invention.

B. Claims 33-132, 145-304 and 367-446 are provisionally rejected as being obvious over claim 18 of U.S. Applications 10/060,523. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '523 and of the instant application recite methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis, whereas the methods of '523 do not provide a specific limitation of the disease to be treated. However, administering the VEGF-2 of SEQ ID NO:2 or 4, or a fragment of ATCC No. 75698 or 97149, to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering

VEGF-2 are the same regardless of the purpose (Ex parte Novitski, 26 USPQ 1391). As claimed, the population of the present invention falls entirely into the population of the present application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

C. Claims 33-132, 145-304 and 367-446 are provisionally rejected under the judicially created doctrine of double patenting over claims 38 and 42-71 of copending Application No. 09/499,468. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '468 and of the instant application recite methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis, whereas the methods of '468 recite methods of stimulating endothelial cell proliferation. However, administering the VEGF-2 of SEQ ID NO:2, or a fragment of ATCC No. 75698 or 97149, to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering VEGF-2 are the same regardless of whether the purpose is to stimulate angiogenesis or proliferation of endothelial cells (Ex parte Novitski, 26 USPQ 1391). Though some claims of '468 define a dosing range, and the claims of the present invention provide a specific population, there would be expected to be overlap in these populations.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

D. Claims 62-89 and 111-150 are provisionally rejected under the judicially created doctrine of double patenting over claim 86 of copending Application No. 10/127,551. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '551 and of the instant application recite methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis, whereas the methods of '551 recite methods of stimulating endothelial cell proliferation. However, administering the VEGF-2 of SEQ ID NO:2 or 4 to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering VEGF-2 are the same regardless of whether the purpose is to stimulate angiogenesis or proliferation of endothelial cells (Ex parte Novitski, 26 USPQ 1391). The present invention defines a population to be treated. However, there would be expected to be overlap in these populations.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

6. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. The rejection of claims 73-84, 93-104, 113-124, 245-256, 285-296 and 326-338 under 35 USC 112, first paragraph regarding an inadequate statement of biological deposit has been withdrawn in view of Applicants' submission of a complete statement.

B. The rejection of claims 145-156, 165-176, 225-236, 245-256, 265-276, 285-296, 407-418 and 427-438 under 35 USC 112, first paragraph, have been withdrawn in view of Applicants arguments and the fact that these fragments can be used as antigens in the production of antibodies.

C. Claims 33-44, 53-64, 73-84, 93-104, 225-236, 245-256, 265-276, 285-296, 367-378, 407-418 and 427-438 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO:2 and 4 and specific fragments thereof, does not reasonably provide enablement for "mature" or "proprotein" forms of SEQ ID NO:2 or 4, or for those proteins having angiogenic activity and which comprise SEQ ID NO:8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

First, the breadth is excessive with regard to Applicants claiming any and all proteins of SEQ ID NO:2 or 4, or produced from ATCC 97149 or 75698 which have angiogenic activity, the only structural requirement being that the protein must comprise SEQ ID NO:8. SEQ ID NO:8 is only 14 residues in length and, of these, only 9 amino acids are known, the remaining 5 residues being "any amino acid." Regardless, Applicants have only provided guidance and working examples of one specific fragment of SEQ ID NO:2 (residues 47-396) which has endothelial cell proliferating activity (Examples 5 and 6). Applicants have not provided any guidance or working examples of any protein, or fragment thereof, of SEQ ID NO:4, or of any fragment which is smaller than that of residues 47-396 of SEQ ID NO:2 which has angiogenic activity, or of any portion of SEQ ID NO:2 with angiogenic activity. Though Applicants do disclose in the specification, as well as in their most recent arguments, that SEQ ID NO:8 is relevant for biological activity, Applicants have not demonstrated that SEQ ID NO:8, or the 8 conserved cysteines, are the only requirements for biological activity, or, more specifically, angiogenesis. The protein of SEQ ID NO:2, for example, is 396 residues. It would not be predictable to the artisan how to make a functional protein, especially one with angiogenic activity, when only given 3.5% of the protein's structure (14/396). Applicants argue that the specification and the Declaration by Dr. Aaronson, teach that residues 108-188 are necessary for biological activity and that page 9, lines 21-25 teach that the 8 cysteine residues are required for function. However, the specification does not teach that these 8 residues, or the residues of SEQ ID NO:8 are the only requirements for biological activity, nor that angiogenesis is one of the biological activities performed by these conserved residues. It appears that Dr. Aaronson's conclusions are based on homology to known proteins and the effect of various regions in these proteins. However, the protein of the '968 patent only shows 30% homology to VEGF (page 2 of the Declaration) and is only homologous to that of Hannink. No functional data has been provided in the specification using this corresponding region of SEQ ID NO:2 or 4 of the present invention. Furthermore, page 9 of the specification only states that the invention *intends to encompass* any protein having these 8 residues and which retains biological activity and that, though the patent by Alitalo et al. also teach that these

conserved regions are required for activity, angiogeneisis does not appear to be one of these activities. Though the claims do not contain the limitation of residues 108-188, adding this limitation will not necessarily overcome this rejection. It is also, respectfully, brought to Applicants attention that numerous proteins require cysteines for functional activity as these proteins are well-known in the art to form bonds with each other which are required to maintain the structure, and therefore, function, of these protein.

Applicants also argue that the specification teaches assay methods to identify biologically active proteins. However, though Applicants may have taught assays methods, they have only provided minimal guidance and working examples of proteins with biological activity. Given only this minimal guidance, and predictability as to what other residues besides 8 conserved cysteine residues and SEQ ID NO:8 are required for this activity, it would be undue experimentation for the artisan to practice the claimed invention.

Applicants have provided no guidance or working examples (i.e. the amino acid sequence) of the "**mature**" form of VEGF-2, nor of any "**proprotein**" of VEGF-2. Applicants have only provided guidance and working examples of the full-length of the VEGF-2 of SEQ ID NO:2. The sequence of any mature form or proprotein has not been disclosed in the specification. In other words, the exact sequence of the mature and proprotein forms are not disclosed in the specification.

Applicant is claiming a very specific species which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Therefore, since these species were not described in the specification, the specification has not enabled one of ordinary skill in the art to make these protein forms. As argued previously, the structure of a "mature form of a polypeptide" cannot be predicted on the basis of the amino acid sequence of the entire protein since the protein may be proteolytically cleaved in vivo, as well as being differentially processed based on which in tissue the protein is expressed. The specification does not evidence isolation or conception of the structure of the "mature form of a polypeptide," or the "preprotein form." Though the "mature" or "proprotein" form of VEGF may be inherent in the structure, these forms can only assumed to be formed in vivo, or in an intact cell system. However, Applicants are claiming an "isolated" protein form. Though Applicants can, respectfully, say that these forms are present in a petry dish full of cells expressing this protein, they have not adequately described the amino structure of these proteins to actually be able to identify these forms in order to isolate them. Therefore, the specification does not enable one of ordinary skill in the art to make the invention as claimed, nor would the structure of these protein forms be predictable to the artisan.

Therefore, there is a lack of guidance and working examples (i.e. the amino acid sequence) of the mature or proprotein forms of VEGF or of any proteins, or fragments thereof, which has angiogenic activity other than residues 47-396 of SEQ ID NO:2. It is also not predictable to the artsian how to make mature or proprotein forms of VEGF-2 given only the protein sequence of SEQ ID NO:2, nor is it predictable which residues are required for angiogenic activity. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention.

*7. **Claim Rejections - 35 USC § 112, first paragraph – written description***

A. The rejection of claims 145-156, 165-176, 225-236, 245-256, 265-276, 285-296, 407-418 and 427-438 under 35 USC 112, first paragraph, have been withdrawn in view of Applicants arguments and the fact that these fragments can be used as antigens in the production of antibodies.

B. Claims 33-44, 53-64, 73-84, 93-104 and 367-378 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 9 of the Office Action dated 8/23/02. Applicants argue that "mature" and "proprotein" are defined on pages 9 and 11 of the specification. Applicants argue that they are inherently in possession of these forms of the proteins and that all the information required to obtain these proteins is provided in the given in the amino acid sequence. They also argue that one in the art could readily envision and identify these proteins. Applicants cite a Declaration by Dr. Aaronson attesting to these facts. However, this Declaration is, respectfully, not found persuasive. The mature or proprotein form of a given protein is of a specific sequence. Though these forms may be inherently formed in a given expression system, for example, the exact sequence is still not known. Therefore, the artisan would not know when they were in possession of the mature or proprotein form of VEGF.

Again, the instant specification fails to describe that portion of a protein which is the "**mature**" portion, or what constitutes a "**proprotein**." Applicant is claiming a very specific species which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As argued previously, the structure of a "mature form of a polypeptide" cannot be predicted on the basis of the amino acid sequence of the entire protein since the protein may be proteolytically cleaved in vivo, as well as being differentially processed based on which in tissue the protein is expressed. The specification does not evidence isolation or conception of the structure of the "mature form of a polypeptide," or the "preprotein form." Though the "mature" or "proprotein" form of VEGF may be inherent in the structure, these forms can only assumed to be formed in vivo, or in an intact cell system. However, Applicants are

claiming an "isolated" protein form. Though Applicants can, respectfully, say that these forms are present in a petry dish full of cells expressing this protein, they have not adequately described the amino structure of these proteins to actually be able to identify these forms in order to isolate them. Therefore, the specification does not provide an adequate written description of a mature protein, or preprotein form and thus the claimed invention, to the extent that it reads upon mature protein or proprotein was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 16, 2003

ROBERT LANDSMAN
PATENT EXAMINER